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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/652,791	08/29/2003	James McSwiggen	03-332-B (400.126)	3409

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/652,791	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2006 and 15 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36,38,48-59,68 and 69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36,38,48-59,68 and 69* is/are rejected.

7)☒ Claim(s) *38* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's responses filed 05/19/2006 and 11/15/2006 have been considered. Rejections and/or objections not reiterated from the previous office action mailed 12/19/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 5/19/2006, claims 36, 38, 48-59 and 68-69 are pending in the application. Applicant has canceled claims 1-35, 37, 39-47 and 60-67.

Priority

As stated in the office action mailed 12/19/2005, applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120. In the instant case, the priority date granted to the amended claims is that of 08/29/2003.

Applicant argues that the present application claims priority to 60/363,124 filed March 11, 2002 because the instantly claimed sequence, SEQ ID No. 225 is recited in provisional application 60/363,124.

Applicant's argument has been considered but is not found persuasive. The provisional application 60/363,124 recites that instantly claimed target, ECGF1, as

Genbank Accession No. NM_001953. It must be noted that NM_001953 is a DNA sequence comprising thymidine nucleotides. The instantly claimed SEQ ID NO. 225. recited in the amendment filed 05/19/2006 and cited in the sequence listing filed 11/15/2006 recites a RNA sequence comprising uridine nucleotides and not thymidine. Therefore, because the prior applications disclose a DNA sequence having Genbank Accession No. NM_001953 and the instantly amended claims recites a RNA sequence having SEQ ID NO. 225, the prior applications do not provide support for the instantly claimed invention.

If Applicant believes the prior application provides support for a RNA sequence claimed as SEQ ID NO. 225, then applicant must point, with particularity, to where such support can be found in the specification of the prior application.

Thus, the instant claims are accorded a priority date of 08/29/2003.

New Claim Objections and Rejections

Specification

The amendments filed 05/19/2006 and 11/15/2006 are objected to under 35 U.S.C. 132(a) because they introduce new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: In the amendment submitted 11/15/2006, Applicants disclose a new sequence listing comprising SEQ ID NO. 225 which applicants state represents Genbank Accession No. NM_001953. The sequence having SEQ ID NO. 225 is a RNA

sequence containing uridine residues whereas Genbank Accession No. NM_001953 submitted in the originally filed application on 08/29/2003 is a DNA sequence as indicated by thymidine residues in the sequence. Therefore, the instant specification does not appear to support the newly submitted RNA sequence having SEQ ID NO. 225 which applicant contends represents Genbank Accession No. NM_001953.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Objections

Claim 38 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 38 depends from claim 36 and recites, "...wherein said siRNA molecule comprises one or more ribonucleotides". The instantly claimed siRNA molecule, by definition, is a short interfering *RNA* molecule and therefore would have at least one ribonucleotide. Therefore, claim 38 fails to further limit claim 36.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36, 38, 48-59 and 68-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, MPEP §2163 states, in part "...a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." Moreover, the written description requirement for a genus may be satisfied through sufficient description of a representative number of species by "...disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between functional and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus."

Instant claim 36 recites "a siRNA molecule...complementary to platelet-derived endothelial cell growth factor (ECGF1) nucleotide sequence corresponding to SEQ ID NO: 225". The instant specification does not define the term "corresponding" and it is not a term of the art. The plain meaning of corresponding is "To be similar or equivalent in character, quantity, origin, structure, or function." (see American Heritage® Dictionary of the English Language, <URL:http:/www.dictionary.reference.com>). Therefore, based on the definition above, one in the art would reasonably include RNAs

similar (i.e. functional equivalents) of SEQ ID NO. 305 in the scope of the claimed invention.

Further, one of ordinary skill in the art would not be able to envision the genus of molecules being instantly claimed because the ECGF1 nucleotide sequence either similar to or equivalent to SEQ ID NO. 225 would have different sequences and therefore siRNA molecules complementary to a ECGF1 nucleotide sequence similar to SEQ ID NO. 225 would be different than siRNA molecules complementary to a ECGF1 nucleotide sequence equivalent to SEQ ID NO. 225.

Therefore, applicant has not described the invention in a way that one of ordinary skill in the art would recognize that Applicant was in possession of the claimed genus at the time of filing.

Claims 36, 38, 48-59 and 68-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 36, 38, 48-59 and 68-69 are drawn to a chemically modified siRNA comprising a sense and an antisense strand wherein the antisense strand is complementary to a sequence corresponding to SEQ ID NO. 225.

The amendment filed 12/19/2006 and the CRF filed 11/15/2006 recite the instant target ECGF1 having Genbank Accession No. NM_001953 as SEQ ID NO. 225. The originally filed specification, on page 136, discloses the instant target ECGF1 as Genbank Accession No. NM_001953, however Genbank Accession No. NM_001953 is a DNA sequence and the newly submitted sequence disclosed as SEQ ID NO. 225 is a RNA sequence. The specification does not contemplate a chemically modified siRNA comprising a sense and an antisense strand wherein the antisense strand is complementary to a RNA sequence corresponding to SEQ ID NO. 225

If Applicant believes that such support is present in the specification and claimed priority documents, Applicant should point, with particularity, to where such support is to be found.

Thus, the instant claims are accorded a priority date of 08/29/2003.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 54-55 and 68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 54-55 and 68 recite a "siRNA molecule" and the claims are indefinite because it is unclear to one of skill in the art which siRNA the claims are referring since the claims depend from the canceled claim 47.

Response to Applicant's Arguments

Re: Double Patenting

Acknowledgement is made of Applicant's consideration of filing a terminal disclaimer upon allowance of the pending claims, therefore the rejection of claims 36, 38, 48-59 and 68-69 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 14-21, 30 and 35-36 of copending Application No. 10/922,034 is maintained.

Re: Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 48, 51-53, 56-60, 62 and 66 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is obviated by the claim amendments filed 12/19/2005.

Re: Claim Rejections - 35 USC § 103

The rejections of record filed 05/19/2006 over claims 37, 40-46 and 60-67 are moot as these claims have been canceled.

The rejection of claims 36, 38, 51-53, 56-59 and 68-69 under 35 U.S.C. 103(a) as being unpatentable over Wyatt et al. (U.S. Patent No: 6,716,975), Hammond et al. (Nature 2001), Tuschl et al. (WO 02/44321), Parrish et al. (Molecular Cell, 2000) and Cook et al. (U.S. Patent No. 5,587,471) is maintained for the reasons of record filed 12/19/2005.

The rejection of claims 36, 38, 48-59 and 68-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wyatt et al. (U.S. Patent No: 6,716,975), Hammond et al. (Nature 2001), Tuschl et al. (WO 02/44321), Parrish et al. (Molecular Cell, 2000) and in further view of Matulic-Adamic (U.S. Patent No. 5,998,203) and Thomson et al. (Nucleic Acids Research 1993) is maintained for the reasons of record filed 12/19/2005.

Applicant's arguments are acknowledged but are not found persuasive. Applicant argues one would not have been motivated to combine antisense art i.e. Wyatt et al. with long double stranded art i.e. Hammond and Parrish et al. to arrive at the presently claimed invention. Applicants further argue Matulic Adamic et al. and Thompson et al. deal with ribozymes and this technology does not apply to siRNA. These arguments are simply not convincing.

At the outset, Wyatt et al. teach an antisense compound directed to an endothelial differentiation gene (EDG1) wherein said antisense reduces expression of said target gene. Wyatt et al. teach such gene plays a role in angiogenesis and if uncontrolled, can lead to numerous pathologic conditions such as cancer (see column 1, line 66 to column 2, line 5). The specification lists the instantly claimed targets on page 136 and teach on page 6, lines 21-30 of the specification that targeting such

ECGF1 genes with dsRNA are useful for modulation of angiogenesis and proliferation of cells such as in disorders such as cancer. While Wyatt et al. does not specifically teach target SEQ ID NO. 225, however Wyatt et al. teach targeting EGF1, a gene having the same function as the instantly claimed gene, ECGF1 and because the instant claims are drawn to siRNA targeted a ECGF1 corresponding to SEQ ID NO. 225, Wyatt et al. teach targeting the instantly claimed sequence based on the plain meaning of "corresponding" as defined above. Further, one of skill in the would have clearly been motivated to substitute a siRNA for the antisense taught by Wyatt et al. for the modulation of target genes associated with angiogenesis and cell proliferation because siRNA has been shown to work more efficiently than antisense in inhibition of gene expression, as stated in the 103 rejection of record filed 12/19/2005.

Regarding Tuschl et al., applicants argue Tuschl et al. teaches away from the use of a 2'-O-methyl in siRNA either individually or in combination with a 2'deoxy-2'-fluoro modification. Applicants further argue Tuschl et al. teach that 2'-O-methyl modifications cannot be used in a siRNA to mediate RNAi and further based on the teachings of Tuschl et al. one of skill in the art would not have been motivated to incorporate 2'-O-methyl modifications into siRNA molecules targeting HER2. Nowhere in the disclosure of Tuschl et al. does it state or give the suggestion that 2'-O-methyl modifications cannot be used in a siRNA or that Tuschl et al. teach one of skill in the art should avoid 2'-O-methyl modifications, as asserted by Applicant. While it is true that Tuschl et al. teach away from extensive 2'-O-methyl modifications of one or both strands of the siRNA, one of skill in the art would have been motivated to incorporate 2'-

O-methyl modifications from the disclosure in Tuschl et al. particularly given what was well known in the art at the time of the instant invention regarding the use of 2'-O-methyl modifications to impart duplex stability and nuclease resistance to oligonucleotides. Applicants have pointed to a section of Tuschl et al. (pages 49-50) for teaching that Tuschl et al. "flatly states that 2'-O-methyl modifications, as are presently claimed, should be avoided." (see remarks filed 08/25/2006 page 11-12). Applicant has based this statement on their interpretation of the sentence "More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi..." wherein the sentence means that the "more extensive" phrase in the sentence applies only to 2'-deoxy and not 2'-O-methyl in the sentence and therefore Tuschl et al. "flatly states" that 2'-O-methyl modifications of siRNA should be avoided. Tuschl et al. does not "flatly state" that one of skill in the art should avoid 2'-O-methyl modifications in siRNA. Tuschl et al. specifically teach in Figure 14 that siRNA with more extensive 2'-deoxy modifications on one or both strands or siRNA with more extensive 2'-O-methyl modifications one or both strands reduced the ability of the siRNAs to mediate RNAi. One of skill in the art would not interpret from those experiments in Figure 14 to mean that 2'-O-methyl would not be a useful modification of siRNA, particularly because it is well know in the art the benefits of incorporating 2'-O-methyl modifications in any nucleic acid for increased stability and nuclease resistance.

Moreover, Tuschl et al. clearly recognize that 2'-modifications enhance the nuclease stability of siRNA molecules and therefore one would have been motivated to search for particular chemical modifications that are tolerated by the siRNA by routine

experimentation of determining the optimum number and placement of the 2'-modifications to see how well the modifications were tolerated with respect to stability and functionality of the siRNA.

Further, applicants argue Parrish et al. teach modifications of long siRNA and do not teach siRNA. Parrish et al. was relied upon to impart stability and nucleic resistance to siRNAs given such modifications had been shown in the art to benefit antisense and ribozymes. Applicant is correct in that Parrish et al. do not teach specifically teach short interfering RNA, however, the modifications taught by Parrish et al. provide stability to a dsRNA that are subsequently involved in RNAi and therefore one of skill in the art would have been motivated to incorporate said modifications into the siRNA taught by Tuschl et al. Moreover, one of skill would recognize that the long dsRNA molecules taught by Parrish et al. were necessarily cleaved into short interfering RNA molecules by Dicer. Applicant goes on to discuss the functional anatomy of long dsRNA as a trigger for RNAi and how the teachings of modifications of long dsRNA do not readily transfer to siRNA. The examiner does not rely on the mechanism of action of long dsRNA taught by Parrish et al. as motivation to incorporate or not incorporate specific modifications into siRNA. Parrish et al. was relied upon solely to state that the nucleotide modifications were known in the art at the time of the instant invention and were known to impart specific benefits to dsRNA.

Applicant's arguments that modifications to ribozymes, as taught by Matulic Adamic et al. and Thompson et al., do not apply to modifications of siRNA are simply not convincing.

Both types of molecules, ribozymes and siRNA, are nucleic acids, a fact acknowledged by applicant (see remarks filed 05/19/2006, page 21) and one of skill in the art would have been motivated to incorporate terminal cap moieties to provide resistance and degradation and further provide motivation to connect sense and antisense strands via a linker to increase efficiency of production of siRNA and stability to siRNA because each of these modifications were known in the art to benefit nucleic acid technologies.

Therefore, as discussed above, in the absence of evidence to the contrary, the invention, as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

The rejection of record of claims 36, 38, 51-53, 56-59 and 68-69 under 35 U.S.C. 103(a) as being unpatentable over Meacci et al. (Biochem 2002), Hammond et al. (Nature 2001), Tuschl et al. (WO 02/44321), Parrish et al. (Molecular Cell, 2000) and Cook et al. (U.S. Patent No. 5,587,471) is maintained for the reasons of record filed 05/19/2006.

Applicant's arguments are acknowledged but are not found persuasive. Applicant argues Meacci et al. deals exclusively with antisense technology and one of skill in the art would not have been motivated to combine the teachings of Tuschl et al. to arrive at the presently claimed invention and further one would not have been motivated to modify a siRNA with the modifications taught by Parrish et al. and Cook et al. to arrive at the presently claimed invention. This is simply not convincing.

One of skill in the art would clearly been motivated to substitute an siRNA for the antisense molecule targeted to an EDG1 as taught by Meacci et al. for the reasons stated upon above for Tuschl et al., Parrish et al. and Cook et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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